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STUDIES ON EFFECT OF JUICES ON DISSOLUTION PROFILE OF PARACETAMOL IN TABLET DOSAGE FORMS

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ABSTRACT

Introduction: The present study was undertaken to examine the effect of beverages such as apple juice, orange juice, pineapple juice, watermelon juice, lemon juice etc. and their interaction on common OTC drug like Paracetamol which is analgesic and antipyretic, usually in the form of an immediate release tablet formulations. Therapeutic effects in terms of the speed and intensity of the analgesic effect is dependent on speed of liberation from formulation. Paracetamol can interact with the food or beverages, which may reduce the drug release, drug absorption in the body and may also lead to an unwanted reaction. **Methods**: *In vitro* Dissolution study was done on these beverages, using phosphate buffer as dissolution media of pH 5.8 with USP Type II apparatus. The samples from dissolution were analyzed under HPLC and UV method. **Results**: The dissolution of drug was found to be less in all of these beverages than in drinking water. It was observed that, when paracetamol is taken with drinking water, maximum drug dissolution takes place i.e. 97.03% and 97.92% by UV spectroscopy and HPLC method respectively as compared to other beverages. The minimum amount of drug release was observed in apple juice i.e. 16.90% and 16.93% by UV spectroscopy and HPLC method respectively when compared with orange, pineapple, watermelon, and lemon juice. The maximum amount of drug release is observed in lemon juice i.e. 39.79% and 43.14% by UV spectroscopy and HPLC method respectively as compared to remaining four juices. **Conclusion**: To get better therapeutic effects without any side effects the drug should be taken with glass of drinking water and avoid taking medicines with beverages. Medicines should not be taken with the meal to avoid any food-drug interactions. The physicians and pharmacists recognize that some foods and drugs, when taken simultaneously, can alter the body's ability to utilize a particular food or drug

KEYWORDS

Beverages, Over-the-counter drug (OTC) and *In vitro* Dissolution etc.

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INTRODUCTON

Food-drug interaction is a broad area and the food which was taken by the patient can affect the rate and extent of drug bioavailability. In recent days tablet which a solid dosage form are the most commonly used one. However, some patients do take medications with beverages other than water.

The US Food and Drug Administration study the effects of food on drug absorption as part of biopharmaceutical characterization of nearly every new drug intended for oral administration.

The Current study was conducted to examine the effect of beverages on common OTC drug. Paracetamol is commonly used as an OTC drug. So to prevent drug-food interaction this study was performed by using paracetamol drug which is act as analgesic and antipyretics[1-3.] Paracetamol (acetaminophen) is one of the most popular and most commonly used drugs around the world, available without a prescription (over-the-counter drug). Paracetamol is available in the market under different brand names such as crocin, calpol and paracip. Out of all these brands crocin was selected for the study. In India people take crocin tablet whenever they feel and at any time for analgesic and antipyretic activity. They may take crocin before or after any other available beverages such as apple juice, orange juice, pineapple juice, watermelon juice, lemon juice etc. Paracetamol can interact with the food or beverages, which may reduce the drug release, drug absorption in the body and may also lead to an unwanted reaction. Hence the study was undertaken to investigate the food drug interaction and effect of various beverages on crocin dissolution[4-6].

MATERIAL

Formic acid, potassium dihydrogen, and sodium hydroxide was purchased from labachem, analab Fine chemicals and Research Lab Fine chemicals respectively.

TABLET MODEL DOSAGE FORM

Paracetamol as active pharmaceutical ingredient purchased from shrikrishna pharmaceuticals and crocin tablet purchased from Sohit Medical Store Bavdhan Pune.

DISSOLUTION STUDY MEDIA

Phosphate buffer (pH 5.8)

It was prepared by mixing of 250ml of potassium dihydrogen phosphate solution and 72ml of sodium hydrogen solution and then make up the volume to 1000ml with distilled water. Water and Juices (apple, orange, pineapple, watermelon, and lemon) were obtained from local store.

METHODS

Preparation of buffer (pH 5.8)

Potassium di-hydrogen phosphate

0.2M-Dissolve 27.21gm of Potassium di hydrogen phosphate in distilled water and make up the volume to 1000ml with distill water.

Sodium hydroxide solution

Dissolve 4gm of NaOH in 100ml distill water and make up the volume up to 500ml with distill water

To prepare 1000ml of phosphate buffer of PH 5.8 take 250ml from solution A and 72ml from solution B. Mix them and make up the volume to 1000ml with distilled water[7].

Calibration curve

25 mg of standard paracetamol was dissolved in 25ml of distilled water (1000ppm) From 1000ppm 1ml of solution was diluted to 10ml of distilled water (100ppm). Further dilutions were made from 100ppm solution to get the following concentration. The different concentrations prepared are 5ppm to 25ppm.

Dissolution

The dissolution characteristics were studied using a paddle apparatus based on a method described in the USP. The dissolution medium was 900ml in volume, maintained at 37.0 ± 5C. Rotation speed of 50rpm was used. Samples of 10ml were withdrawn from the dissolution medium at appropriate time intervals and filtered through a membrane filter (pore size 0.45µ). Each experiment was carried out using three tablets. The samples obtained from dissolution study were diluted with mobile phase. The absorbance was measured by a spectrophotometer (Carry 100) at 243 nm. The experiment was carried out in a phosphate buffer medium at pH 5.8[7].

High performance liquid chromatography (HPLC)

Jasco HPLC was used. Column used in the HPLC was C18 (Kromacil-100-5C-18 250*4.6mm). Detector used in the HPLC was photo diode array detector (PDA).

Mobile phase-Methanol of HPLC grade and distilled water was used in the ratio of 3:1.

The sample obtain from dissolution were filtered through whattman filter paper by using vacuum filtration. 1 ml sample was pipette out and diluted to 10ml with mobile phase. The samples were then injected into the column. Injected samples were scan at 243nm[8].

Ultra-violet visible spectrophotometer (UV)

Varian spectrophotometer was used of model Cary 100. The detector used in spectrophotometer was photo diode array detector (PDA).

The samples obtained from dissolution study were filtered through whattman filter paper by using vaccum filtration. 1 ml of filtered sample was pipette out and diluted with the mobile phase in the ratio of 3:1. The samples further diluted to get clear solution. Diluted samples were then scan at 243nm[8].

PROCEDURE FOR SAMPLES ANALYSIS

Phosphate buffer

Type-2 apparatus was used for dissolution study. 900ml of phosphate buffer of pH 5.8 was used as media. The temp of vessel was maintained at 37ºC ± 5ºC. The rpm of apparatus was set at 50rpm. 500mg of paracetamol (Crocin tablet) was introduced in three vessels and one vessel was kept as blank. Sample up to 10ml was withdrawn from three respective vessels at specific time interval i.e. 15min, 30min, 45min, 60min, 90min, 120min. The same amount of sample was replaced with fresh aliquot from blank vessel. The samples obtained were filter through whattman filter paper (pore size 0.3µ) using vacuum filter pump.

HPLC

The samples obtained from dissolution apparatus was diluted using mobile phase.1ml of filtered sample was diluted with 10ml of mobile phase; water: methanol in the ratio of (3:1). The diluted samples were then injected in to column (C18) through injector. The injected samples were scanned at 243nm.

UV

The samples obtained from dissolution apparatus was diluted using mobile phase.1ml of filtered sample was diluted with 10ml of mobile phase; water: methanol in the ratio of (3:1). The diluted samples were examined under UV at 243nm using photo Diode Array (PDA) detector.

Water

Dissolution study was done by using rotating paddle apparatus. 650ml of phosphate buffer of pH 5.8 was used as media. 250ml of drinking water as sample was added in 650ml of phosphate buffer to make 900ml volume. The temp of vessel was maintained at 37ºC ± 5ºC. The rpm of apparatus was set at 50rpm. 500mg of paracetamol (Crocin tablet) was introduced in three vessels and one vessel was kept as blank. Sample up to 10ml was withdrawn from three respective vessels at specific time interval i.e. 15min, 30min, 45min, 60min, 90min, 120min. The same amount of sample was replaced with fresh aliquot from blank vessel. The samples obtained were filter through whattman filter paper (pore size 0.3µ) using vacuum filter pump.

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Apple Juice

Type-2 apparatus was used for dissolution study. 650ml of phosphate buffer of pH 5.8 was used as media. 250ml of fresh apple juice as sample was added in 6500ml of phosphate buffer to make 900ml volume. The temp of vessel was maintained at 37ºC ± 5ºC. The rpm of apparatus was set at 50rpm. 500mg of paracetamol (Crocin tablet) was introduced in three vessels and one vessel was kept as blank. Sample up to 10ml was withdrawn from three respective vessels at specific time interval i.e. 15min, 30min, 45min, 60min, 90min, 120min. The

same amount of sample was replaced with fresh aliquot from blank vessel. The samples obtained were filter through whattman filter paper (pore size 0.3μ) using vacuum filter pump.

HPLC

The samples obtained from dissolution apparatus was diluted using mobile phase.1ml of filtered sample was diluted with 10ml of mobile phase; water: methanol in the ratio of (3:1). The diluted sample was then injected in to column (C18) through injector. The injected samples were scanned at 243nm.

UV

The samples obtained from dissolution apparatus was diluted using mobile phase. 1ml of filtered sample was diluted with 10ml of mobile phase; water: methanol in the ratio of (3:1). The diluted samples were examined under UV at 243nm using photo Diode Array (PDA) detector.

Orange Juice

Dissolution study was done by using rotating paddle apparatus. 6500ml of phosphate buffer of pH 5.8 was used as media. 250ml of fresh orange juice as sample was added in 6500ml of phosphate buffer to make 900ml volume. The temp of vessel was maintained at 37ºC ± 5ºC. The rpm of apparatus was set at 50rpm. 500mg of paracetamol (Crocin tablet) was introduced in three vessels and one vessel was kept as blank. Sample up to 10ml was withdrawn from three respective vessels at specific time interval i.e. 15min, 30min, 45min, 60min, 90min, 120min. The same amount of sample was replaced with fresh aliquot from blank vessel. The samples obtained were filter through whattman filter paper (pore size 0.3μ) using vacuum filter pump.

HPLC

The samples obtained from dissolution apparatus was diluted using mobile phase.1ml of filtered sample was diluted with 10ml of mobile phase; water: methanol in the ratio of (3:1). The diluted samples were then injected in to column (C18) through injector. The injected samples were scanned at 243nm.

UV-The samples obtained from dissolution apparatus was diluted using mobile phase.1ml of filtered sample was diluted with 10ml of mobile phase; water: methanol in the ratio of (3:1). The diluted samples were examined under UV at 243nm using photo Diode Array (PDA) detector.

Pineapple Juice

Type-2 apparatus was used for dissolution study. 650ml of phosphate buffer of pH 5.8 was used as media. 250ml of fresh pineapple juice as sample was added in 650ml of phosphate buffer to make 900ml volume. The temp of vessel was maintained at 37ºC ± 5ºC. The rpm of apparatus was set at 50rpm. 500mg of paracetamol (Crocin tablet) was introduced in three vessels and one vessel was kept as blank. Sample up to 10ml was withdrawn from three respective vessels at specific time interval i.e. 15min, 30min, 45min, 60min, 90min, 120min. The same amount of sample was replaced with fresh aliquot from blank vessel. The samples obtained were filter through whattman filter paper (pore size 0.3μ) using vacuum filter pump.

HPLC

The samples obtained from dissolution apparatus was diluted using mobile phase.1ml of filtered sample was diluted with 10ml of mobile phase; water: methanol in the ratio of (3:1). The diluted samples were then injected in to column (C18) through injector. The injected samples were scanned at 243nm.

UV

The samples obtained from dissolution apparatus was diluted using mobile phase.1ml of filtered sample was diluted with 10ml of mobile phase; water: methanol in the ratio of (3:1). The diluted samples were examined under UV at 243nm using photo Diode Array (PDA) detector.

Watermelon Juice

Type-2 apparatus was used for dissolution study. 650ml of phosphate buffer of pH 5.8 was used as media. 250ml of fresh watermelon juice as sample was added in 650ml of phosphate buffer to make 900ml volume. The temp of vessel was maintained at 37ºC ± 5ºC. The rpm of apparatus was set at 50rpm. 500mg of paracetamol (Crocin tablet) was introduced in three vessels and one vessel was kept as blank. Sample up to 10ml was withdrawn from three respective vessels at specific time interval i.e.

15min, 30min, 45min, 60min, 90min, 120min. The same amount of sample was replaced with fresh aliquot from blank vessel. The samples obtained were filter through whattman filter paper (pore size 0.3 μ) using vacuum filter pump.

HPLC

The samples obtained from dissolution apparatus was diluted using mobile phase.1ml of filtered sample was diluted with 10ml of mobile phase; water: methanol in the ratio of (3:1). The diluted samples were then injected in to column (C18) through injector. The injected samples were scanned at 243nm.

UV

The samples obtained from dissolution apparatus was diluted using mobile phase.1ml of filtered sample was diluted with 10ml of mobile phase; water: methanol in the ratio of (3:1). The diluted samples were examined under UV at 243nm using photo Diode Array (PDA) detector.

Lemon Juice

Dissolution study was done by using rotating paddle apparatus. 650ml of phosphate buffer of pH 5.8 was used as media. 250ml of lemon juice as sample was added in 650ml of phosphate buffer to make 900ml volume. The temp of vessel was maintained at 37ºC ± 5ºC. The rpm of apparatus was set at 50rpm. 500mg of paracetamol (Crocin tablet) was introduced in three vessels and one vessel was kept as blank. Sample up to 10ml was withdrawn from three respective vessels at specific time interval i.e. 15min, 30min, 45min, 60min, 90min, 120min. The same amount of sample was replaced with fresh aliquot from blank vessel. The samples obtained were filter through whattman filter paper (pore size 0.3μ) using vacuum filter pump.

HPLC M

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UV

The samples obtained from dissolution apparatus was diluted using mobile phase.1ml of filtered sample was diluted with 10ml of mobile phase; water: methanol in the ratio of (3:1). The diluted samples were examined under UV at 243nm using photo Diode Array (PDA) detector.

RESULTS AND DISCUSSION

Calibration curve of Paracetamol by Ultra-violet spectrophotometer[9,10]

25 mg standard drug (Paracetamol) was dissolved in 25ml distilled water (1000ppm) to get standard stock solution (SSS). Form SSS, 1ml solution was transferred to 10 ml flask and diluted to 10 ml with methanol and water in the ration of 75: 25% v/v (100ppm). The absorbance of various concentration of paracetamol by UV and HPLC is shown in Table No.1 and 2 respectively. The absorbance curve of paracetamol by UV and HPLC is shown in Figure No.1 and 2 respectively. The standard paracetamol graph is shown in Figure No.3.

Figure No.4 and Figure No.5 represents overlay data of UV and HPLC of all samples of juices.

SUMMARY AND CONCLUSION

Summary

The Current study was conducted to examine the effect of beverages on general OTC drug. The intent of the study was to prevent food-drug interactions. Paracetamol is commonly used OTC drug. Its molecular weight is 151.2 and half-life of drug is 1-4 hrs. It is largely used as analgesic and antipyretics. It is generally used as painkiller. The aim of this work is simulated dissolution to study fruit juices effects on OTC product containing paracetamol[11-13].

The paracetamol has compliance for color and appearance as mentioned in its profile. From UV analysis of drug, it was observed that λ max of paracetamol was 243nm with slope (m) 0.0538 and correlation coefficient of 0.992. From HPLC analysis of drug it was observed that λ max of paracetamol was 243nm with slope (m) 48859 and correlation coefficient of 0.997. Beverages like apple juice, orange juice, pineapple juice,

watermelon juice and lemon juice were used for the study. Dissolution study was done using these beverages, using phosphate buffer as media of pH 5.8. The samples from dissolution were analyzed under HPLC and UV.

Phosphate Buffer

500mg of paracetamol was used for dissolution containing potassium di hydrogen buffer as media of pH 5.8, volume 900ml. The samples were analyzed under UV and HPLC. It was found that in phosphate buffer the maximum drug release was observed at 120min i.e. 93.43% and 94.51%.

Water

A glass of water (200ml) was used to study the drug release. It was found that the maximum drug release of water on UV and HPLC was 97.03% and 97.92% at 120min.

Apple juice

It was found that the maximum drug release in apple juice was observed at 120min i.e. 16.90% on UV and 16.93% on HPLC. Apple juice contains various minerals such as potassium, calcium, phosphorus, and magnesium, plus smaller amounts of iron, manganese, copper, and zinc. It also contains several B vitamins and vitamin C. Paracetamol might be forming a complex with one or more ingredients of apple juice, which may be retarding the paracetamol dissolution in the medium.

Orange juice

In orange juice the maximum percent drug release of paracetamol on UV was observed to 28.29% and on HPLC it was found to 26.83%. Orange juice contain bioflavonoid-hesperidin, potassium citrate, citric acid, thiamine and dietary fibers. It also contains *potassium, thiamin,* and *folate.* Paracetamol might be forming a complex with one or more ingredients of orange juice, which may be affecting the paracetamol dissolution in the medium.

Pineapple juice

It is observed that in pineapple juice the percent drug release of paracetamol is less as compared to phosphate buffer, water, orange juice. The maximum percent drug release was found to 26.76% at 120min on UV and 26.16% on HPLC at 120mn. Pineapple juice contains vitamin C, B-Complex (folate, thiamine, pyridoxine, riboflavin). It contains minerals like potassium, calcium, phosphorous and Manganese. Paracetamol will might be forming a conjugation with one or more ingredients of pineapple juice, which may reduce the absorption of paracetamol in the medium.

Watermelon juice

Watermelons contain high quantities of minerals, vitamins, antioxidants, and phytonutrients. Watermelons also provide a good amount of dietary fiber, carbohydrate and protein. So paracetamol may be forming a complex with one or more ingredients of watermelon juice, which may be retarding the paracetamol dissolution in the medium. The maximum absorption of drug in watermelon juice was found to be 39.34% on UV and on HPLC it was 34.2%.

Lemon juice

Maximum drug release of crocin tablet in lemon juice on UV and HPLC was observed to 39.79% and 43.14%. As compared to apple, orange, pineapple and watermelon juice the percent drug release is more in lemon juice. The lemon juice mainly contains fruit acids, mainly citric acid (8%) and sugars. Lemon juice contain various phytochemicals, including polyphenols, terpenes, and tannins. Paracetamol may be form a complex with one or more ingredients of lemon juice, which might be retarding the paracetamol dissolution in the medium[14-18].

Table No.1: Calibration curve (UV)

S.No	Conc. in(ml)	Conc. in (ppm)	Absorbance
1	0.5	5	0.395
2	1	10	0.588
3	1.5	15	0.888
4	2	20	1.148
5	2.5	25	1.459

Calibration curve of Paracetamol by High Performance Liquid Chromatography (HPLC)

Table No.2: Calibration curve HPLC

S.No	Conc. in (ml)	Conc. in (ppm)	Area
1	0.5	5	249740
2	1	10	491480
3	1.5	15	721248
4	2	20	962971
5	2.5	25	1264295
6	3	30	1443593

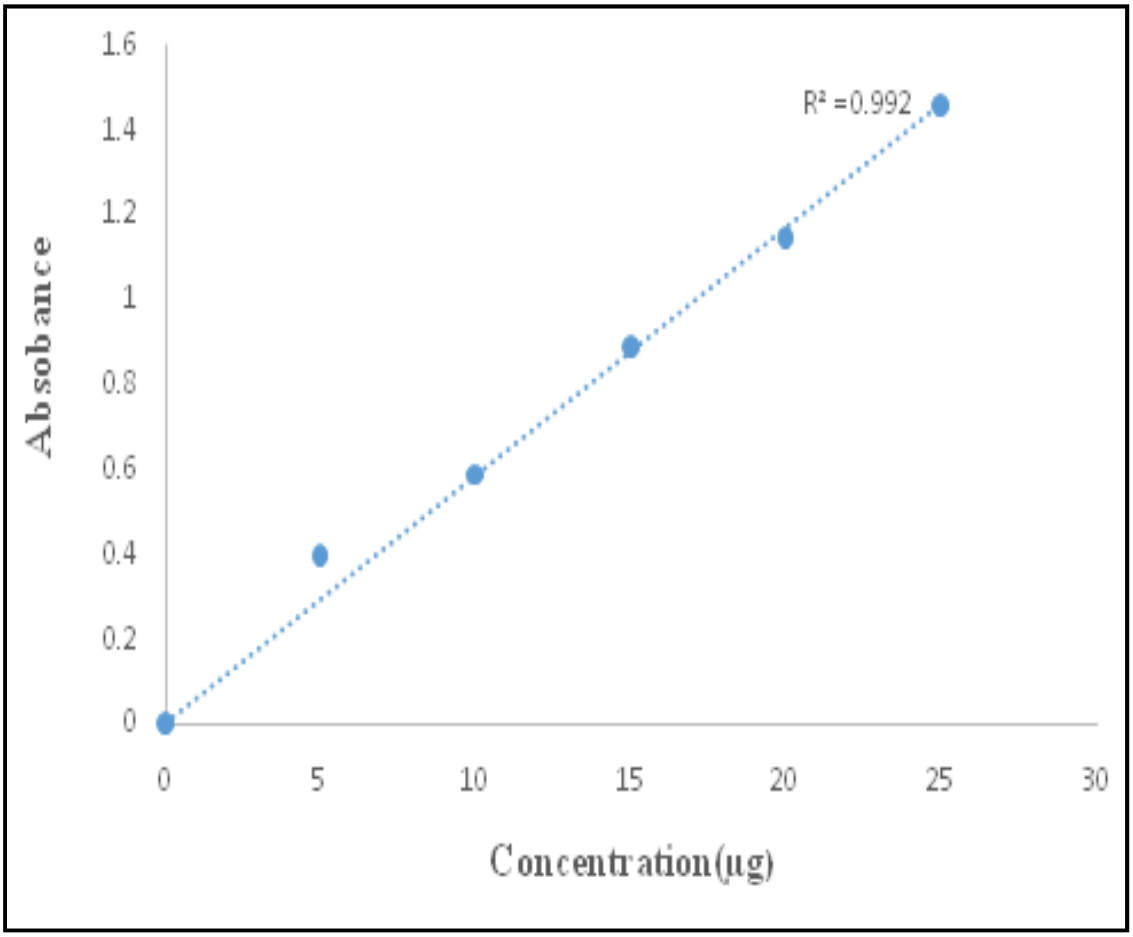

Figure No.1: Calibration curve UV

Intercept(C) and slope (M) was 0.892 and 0.0538 obtained

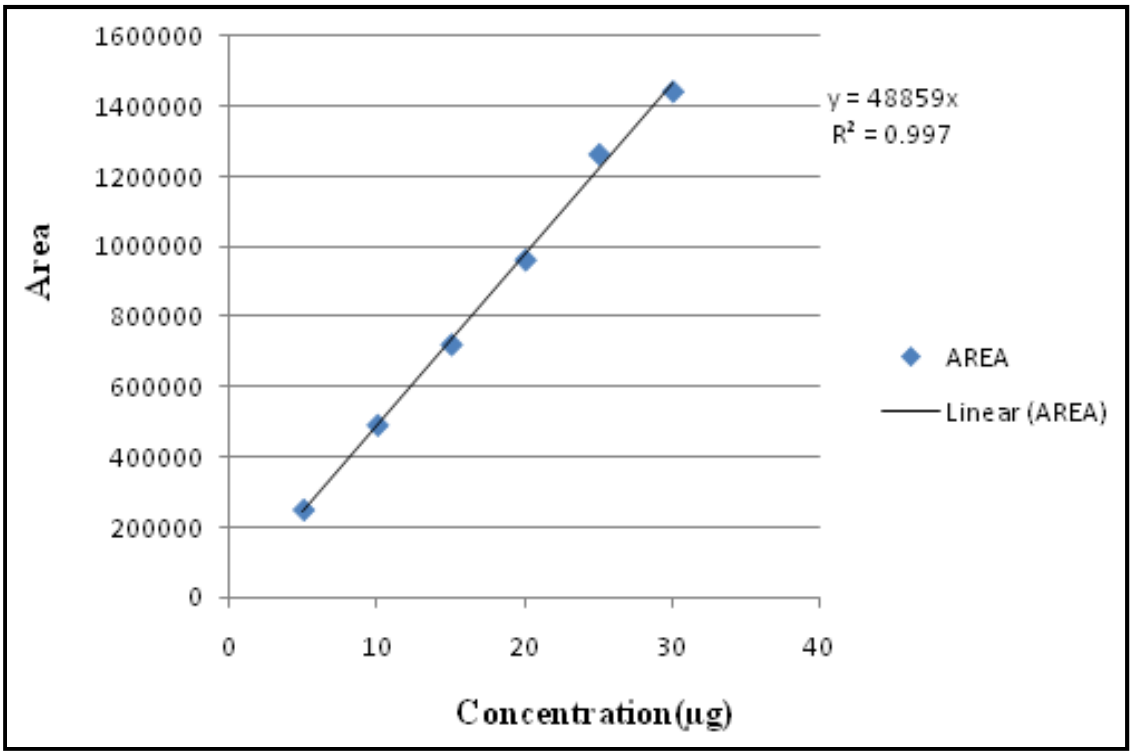

Figure No.2: Calibration curve of HPLC of standard Paracetamol

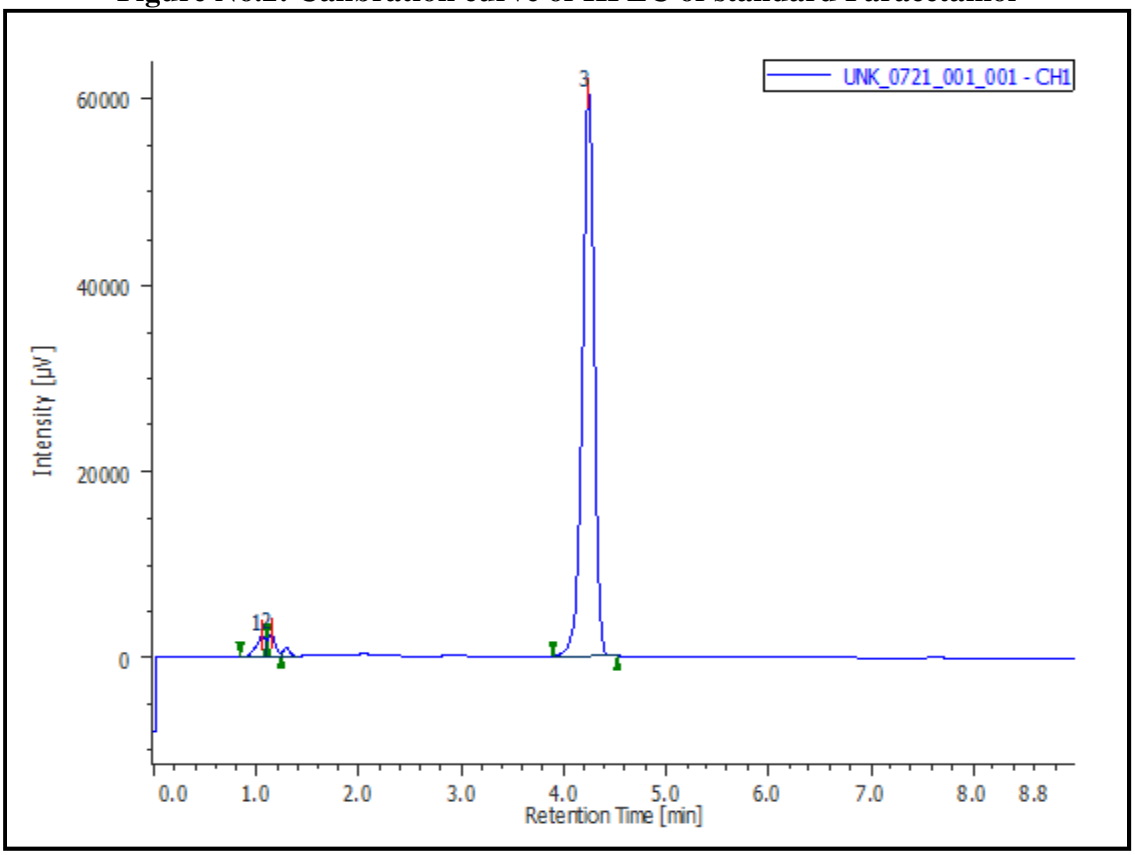

Figure No.3: Standard graph of pure Paracetamol

UV Analysis

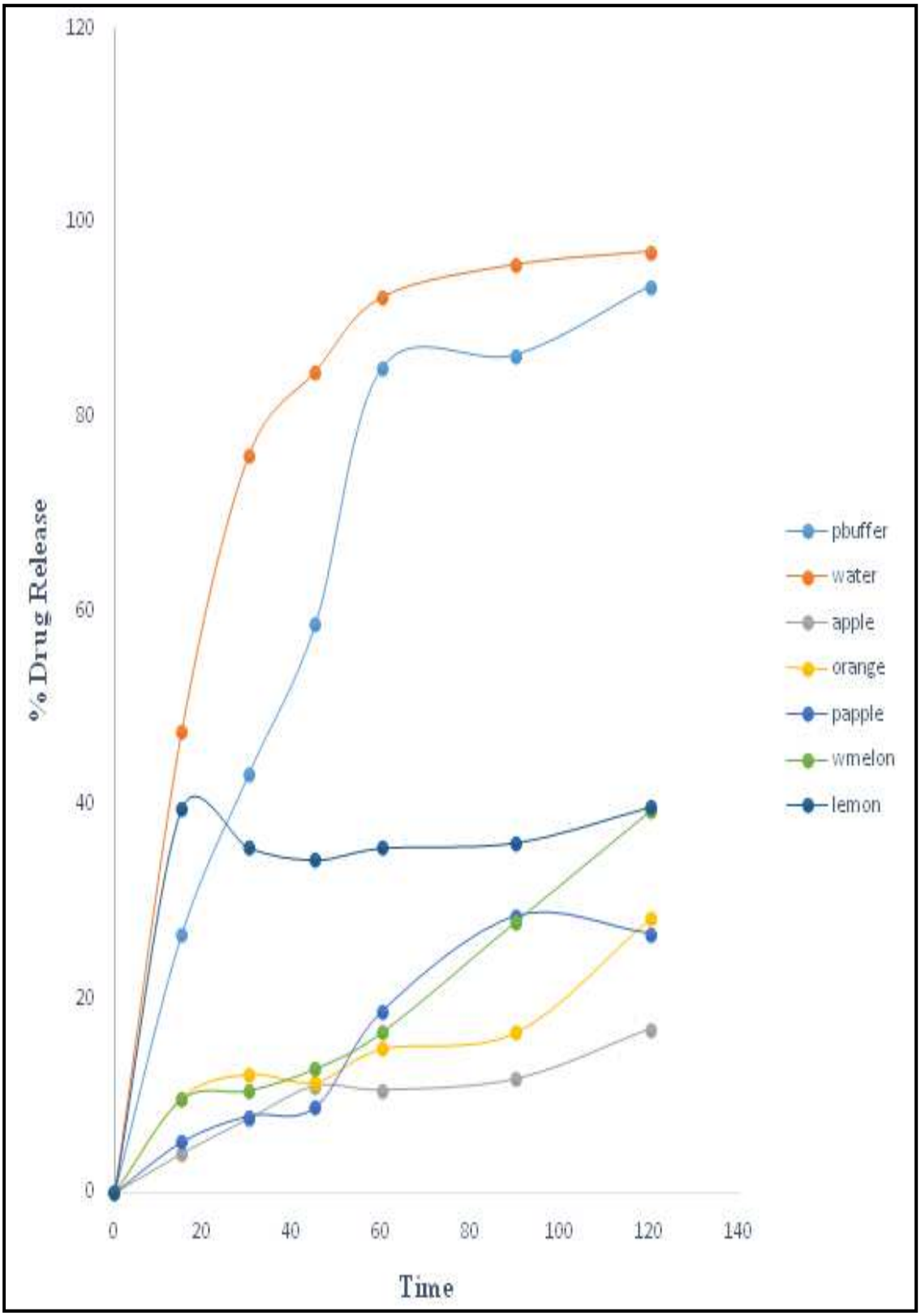

Figure No.4: Overlay Graph of UV data

HPLC Analysis

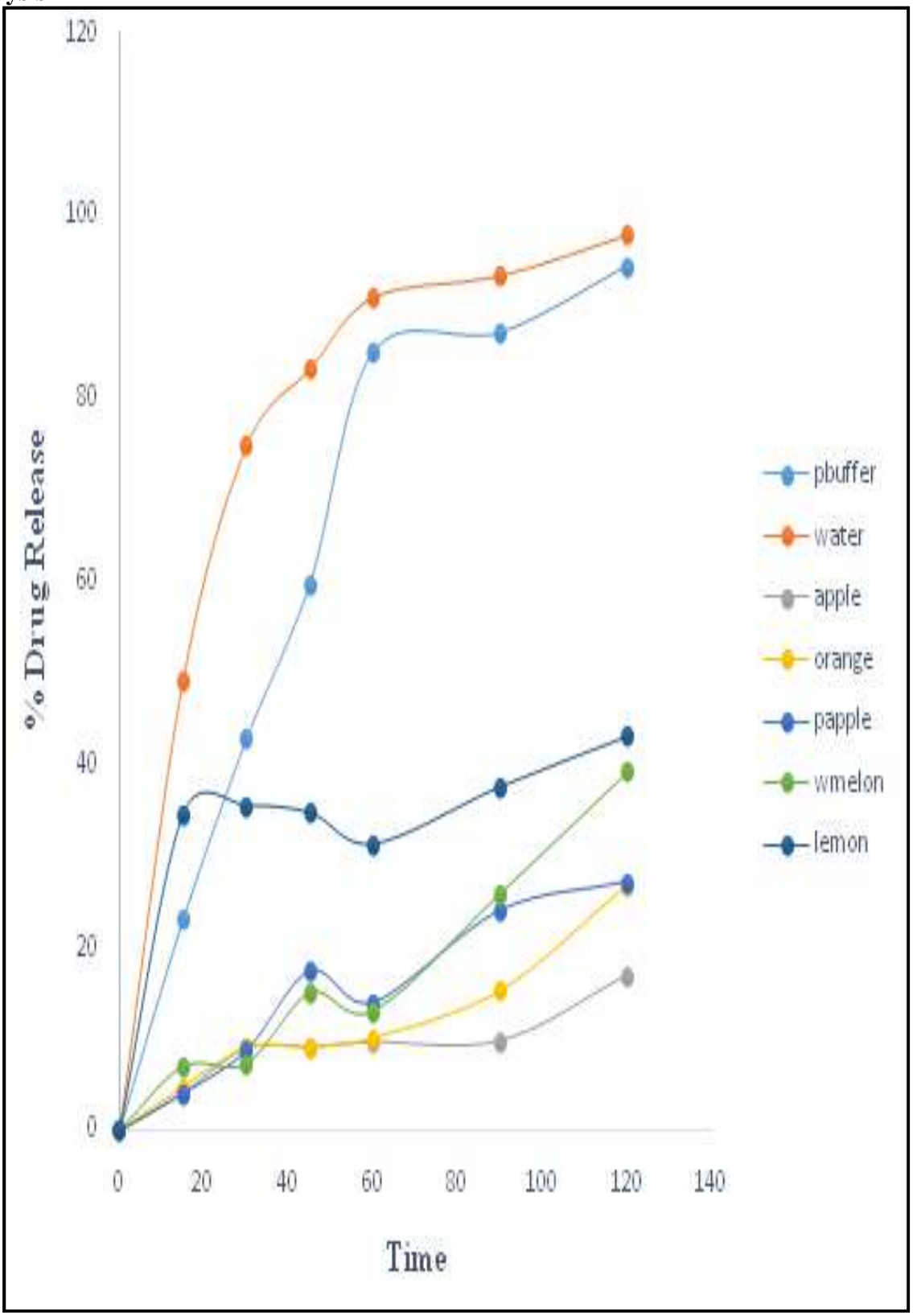

Figure No.5: Overlay Graph of HPLC data

CONCLUSION

Medicines can treat and cure many health problems. If proper care is not taken while administrating the medicines, then it may cause serious side effects. Medicines should have the predictable effect and its activity should not be affected by the food or beverages taken along with the medicines. The present study was undertaken to examine the effect of beverages such as apple juice, orange juice, pineapple juice, watermelon juice, lemon juice etc. and their interaction on common OTC drug like Paracetamol which is analgesic and antipyretic, usually in the form of an immediate release tablet formulations. A nutrition status of the patient may get altered by the food-drug interactions and may result into adverse drug reactions. Drug interactions should be avoided. Paracetamol is broadly used OTC drug; it should be taken with water instead of any other beverages to get better therapeutic effect. Paracetamol might have any chemical interactions with contents present apple juice, orange juice, pineapple juice, watermelon juice and lemon juice. So the dissolution of drug is found to be less in all of these beverages. It is observed that, when paracetamol is taken with water, maximum drug dissolution takes place as compared to other beverages. The minimum dissolution of drug is obtained in apple juice if compared with orange, pineapple, watermelon, and lemon juice. The maximum amount of drug release is observed in lemon juice as compared to remaining four juices. To get better therapeutic effects without any side effects the drug should be taken with glass of water and avoid taking medicines with beverages. Medicines should be taken before or after half an hour of meal to avoid any food- drug interactions. To determine the precise interaction between contents present in beverages and paracetamol further detail study is required.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest in publication of this paper.

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